erythrokeratodermia variabilis et progressiva

Erythrokeratodermia variabilis et progressiva (EKVP) is a skin disorder that is present at birth or becomes apparent in infancy. Although its signs and symptoms vary, the condition is characterized by two major features. The first is areas of hyperkeratosis, which is rough, thickened skin. These thickened patches are usually reddish-brown and can either be widespread over many parts of the body or occur only in a small area. They tend to be fixed, meaning they do not spread or go away. However, the patches can vary in size and shape, and in some affected people they get larger over time. The areas of thickened skin are generally symmetric, which means they occur in the same places on the right and left sides of the body.

The second major feature of EKVP is patches of reddened skin called erythematous areas. Unlike the hyperkeratosis that occurs in this disorder, the erythematous areas are usually transient, which means they come and go. They vary in size, shape, and location, and can occur anywhere on the body. The redness can be triggered by sudden changes in temperature, emotional stress, or trauma or irritation to the area. It usually fades within hours to days.

Frequency

EKVP is a rare disorder; its prevalence is unknown.

Genetic Changes

EKVP can be caused by mutations in the *GJB3* or *GJB4* gene. These genes provide instructions for making proteins called connexin 31 and connexin 30.3, respectively. These proteins are part of the connexin family, a group of proteins that form channels called gap junctions on the surface of cells. Gap junctions open and close to regulate the flow of nutrients, charged atoms (ions), and other signaling molecules from one cell to another. They are essential for direct communication between neighboring cells. Gap junctions formed with connexin 31 and connexin 30.3 are found in several tissues, including the outermost layer of skin (the epidermis).

The *GJB3* and *GJB4* gene mutations that cause EKVP alter the structure of the connexins produced from these genes. Studies suggest that the abnormal proteins can build up in a cell structure called the endoplasmic reticulum (ER), triggering a harmful process known as ER stress. Researchers suspect that ER stress damages and leads to the premature death of cells in the epidermis. This cell death leads to skin inflammation, which appears to underlie the development of erythematous areas. The mechanism by which epidermal damage and cell death contributes to hyperkeratosis is poorly understood.

In some cases, affected individuals have no identified mutation in the *GJB3* or *GJB4* gene. In these individuals, the cause of the disorder is unknown. Researchers suspect that changes in other, unidentified genes may also be associated with EKVP.

Inheritance Pattern

EKVP is most often inherited in an autosomal dominant pattern, which means one copy of an altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person inherits the mutation from one affected parent. Other cases result from new gene mutations and occur in people with no history of the disorder in their family.

A few studies have suggested that EKVP can also have an autosomal recessive pattern of inheritance. However, this inheritance pattern has only been reported in a small number of affected families, and not all researchers agree that it is truly autosomal recessive. Autosomal recessive inheritance means both copies of a gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- EKV
- EKV-P
- EKVP
- erythrokeratodermia variabilis
- erythrokeratodermia variabilis of Mendes da Costa
- erythrokeratodermia, progressive symmetric
- progressive symmetrical erythrokeratoderma of Gottron

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Erythrokeratodermia variabilis
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0265961/

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html

- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Health Topic: Skin Conditions
  https://medlineplus.gov/skinconditions.html

Genetic and Rare Diseases Information Center

- Erythrokeratodermia variabilis et progressiva
  https://rarediseases.info.nih.gov/diseases/10923/erythrokeratodermia-variabilis-et-progressiva

Educational Resources

- Disease InfoSearch: Erythrokeratodermia variabilis et progressiva
  http://www.diseaseinfosearch.org/Erythrokeratodermia+variabilis+et+progressiva/8359
- MalaCards: erythrokeratodermia variabilis et progressiva
  http://www.malacards.org/card/erythrokeratodermia_variabilis_et_progressiva
- Orphanet: Erythrokeratodermia variabilis
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=317
- Orphanet: Progressive symmetric erythrokeratodermia
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=316

Patient Support and Advocacy Resources

- Foundation for Ichthyosis and Related Skin Types (FIRST)
  http://www.firstskinfoundation.org/content.cfm/Ichthyosis/Erythrokeratoderma-Variablis-EKV/page_id/546
- Ichthyosis Support Group (UK)
  http://www.ichthyosis.org.uk/ekv-erythrokeratoderma-variabilis/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28Erythrokeratodermia+Variabilis%5BMAJR%5D%29+OR+%28Erythrokeratodermia+Variabilis%5BTI%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D

OMIM

- ERYTHROKERATODERMIA VARIABILIS ET PROGRESSIVA
  http://omim.org/entry/133200

Sources for This Summary

- Chi J, Li L, Liu M, Tan J, Tang C, Pan Q, Wang D, Zhang Z. Pathogenic connexin-31 forms constitutively active hemichannels to promote necrotic cell death. PLoS One. 2012;7(2):e32531. doi: 10.1371/journal.pone.0032531. Epub 2012 Feb 29.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22393412
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3290583/
- Fuchs-Telem D, Pessach Y, Mevorah B, Shirazi I, Sarig O, Sprecher E. Erythrokeratoderma variabilis caused by a recessive mutation in GJB3. Clin Exp Dermatol. 2011 Jun;36(4):406-11. doi: 10.1111/j.1365-2230.2010.03986.x.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21564177
- Gottfried I, Landau M, Glaser F, Di WL, Ophir J, Mevorah B, Ben-Tal N, Kelsell DP, Avraham KB. A mutation in GJB3 is associated with recessive erythrokeratodermia variabilis (EKV) and leads to defective trafficking of the connexin 31 protein. Hum Mol Genet. 2002 May 15;11(11):1311-6.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12019212
- Macari F, Landau M, Cousin P, Mevorah B, Brenner S, Panizzon R, Schorderet DF, Hohl D, Huber M. Mutation in the gene for connexin 30.3 in a family with erythrokeratodermia variabilis. Am J Hum Genet. 2000 Nov;67(5):1296-301. Epub 2000 Oct 3.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11017804
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1288569/
- Richard G, Brown N, Rouan F, Van der Schroeff JG, Bijlsma E, Eichenfield LF, Sybert VP, Greer KE, Hogan P, Campanelli C, Compton JG, Bale SJ, DiGiovanna JJ, Uitto J. Genetic heterogeneity in erythrokeratodermia variabilis: novel mutations in the connexin gene GJB4 (Cx30.3) and genotype-phenotype correlations. J Invest Dermatol. 2003 Apr;120(4):601-9.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12648223
- Richard G, Smith LE, Bailey RA, Itin P, Hohl D, Epstein EH Jr, DiGiovanna JJ, Compton JG, Bale SJ. Mutations in the human connexin gene GJB3 cause erythrokeratodermia variabilis. Nat Genet. 1998 Dec;20(4):366-9.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/9843209
- van Steensel MA, Oranje AP, van der Schroeff JG, Wagner A, van Geel M. The missense mutation G12D in connexin30.3 can cause both erythrokeratodermia variabilis of Mendes da Costa and progressive symmetric erythrokeratodermia of Gottron. Am J Med Genet A. 2009 Feb 15;149A(4): 657-61. doi: 10.1002/ajmg.a.32744.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19291775

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/condition/erythrokeratodermia-variabilis-et-progressiva

Reviewed: January 2014
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
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National Institutes of Health
Department of Health & Human Services